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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/774,122	02/06/2004	Thomas P. Zwaka	960296.99021	8384

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EXAMINER	
MARVICH, MARIA	
ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/774,122	ZWAKA ET AL.	
	Examiner	Art Unit	
	MARIA B. MARVICH	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-18* is/are pending in the application.

4a) Of the above claim(s) *5,6,11 and 14-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,7-10,12, 13, 17 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/16/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1 and 3-18 are pending in the instant action. Claims 5, 6, 11 and 14-16 are withdrawn. Therefore, claims 1, 3, 4, 7-10, 17 and 18 are under examination in this action.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/16/08 has been entered.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 4, 7-10, 17 and 18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. **This is a new rejection based.**

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a

conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

The instant claims are drawn to methods of performing targeted modifications of human embryonic stem (ES) cells, by introduction of a genetic construct into human ES cells in culture wherein the construct includes a marker gene for cellular identification for homologous recombination, followed by electroporation. The methods are quite broadly drawn to any method of electroporation. In traverse of claim rejections under 35 U.S.C. 103 as being obvious over Benvensity et al in view of West et al, on pages 6-8 of the amendment filed 4/16/08, applicants' argue that the methods of Benvenisty et al for electroporation of hES cells are not robust enough to allow for further manipulation. As part of their response, applicants have submitted a copy of a Declaration filed by Dr. Benvenisty in an unrelated application on 10/27/2004 (it is noted that the Declaration has been provided as part of the IDS filed 4/16/08, the Declaration has been considered but has been crossed off of the 1449). Relevant to applicants' instant arguments is a statement by Benvensity et al that "Although the Examiner points out that our application states that "human ES' cells " can be transfected by electroporation ..." these were our own observations, not those reported by others working in the field. However, it should be emphasized that the yield obtained then (at the time of the present invention) when transfecting hES cell through electroporation was not feasible for performing further manipulations with the transfected cells and thus, we abandoned this technology and searched for a substitute. Except for other publications from my laboratory, no other researcher reported successful transfection of human ES cells under the same conditions described in the present

application, until the Zwaka et al. reference in 2003, a full three years after the priority date of this application, in spite of the wealth of information available concerning how to achieve successful transfection of ES cells in other animals, or how to achieve transfection of other cell types in both humans and other animals." However, the instant claims are not directed to any particular method of electroporation. Rather, the instant claims are directed quite broadly to any method of electroporation. The MPEP 716.02 states "Any differences between the claimed invention and the prior art may be expected to result in some differences in properties. The issue is whether the properties differ to such an extent that the difference is really unexpected." The instant specification appears to only teach this method

"One week before electroporation, cells were plated onto matrigel (Becton Dickinson) coated 10 cm dishes and cultured with murine embryonic fibroblast conditioned media supplemented with 4 ng/ml basic fibroblast growth factor. For electroporation, cells were harvested with collagenase IV (1 mg/ml, Invitrogen) for 7 min at 37°C, washed with medium, and resuspended in 0.5 ml culture medium (1.5-3.0x107 cells). Just prior to electroporation, 0.3 ml phosphate buffered saline (PBS, Invitrogen) containing 40 mg linearized targeting vector DNA was added. Cells were then exposed to a single 320 V, 200 #F pulse at room temperature using the BioRad Gene Pulser II (0.4 cm gap cuvette). Cells were incubated for 10 minutes at room temperature and were plated at high density on matrigel."

As taught by MPEP 2145, "Various limitations on which appellant relied were not stated in the claims; the specification did not provide evidence indicating these limitations must be read into the claims to give meaning to the disputed terms." Thus, it is not clear that electroporation is limited to these methods as opposed to any other methods of electroporation such as those that applicants argue are not enabled. In other words, applicants' claims encompass methods that are according to Benvensity not enabled.

The invention recites use of a broad group of methods of electroporation to transform hES cells. Given the unpredictability of the art, the lack of adequate working examples and the lack of guidance provided by applicants as to what steps distinguish the recited method from

other non-enabled ones, the skilled artisan would have to have conducted undue, unpredictable experimentation to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4, 7, 8, 10, 10, 12, 17 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Smith et al (US 6,146,888; see entire document). **This is a new rejection.**

Smith et al teach use of a targeting construct to be used in homologous recombination. The vector is shown in figure 3 and comprises 5' and 3' flanking arms for homologous recombination as well as a marker to be selectively targeted to human ES cells (see e.g. bridging ¶, Col 1-2). The marker comprises a promoter that is selectively active in specific cell types (see e.g. claim 11). By transforming the cell with the marker construct and allowing homologous recombination to occur, cells can be purified that selectively express the marker such as by FACS (see e.g. col 3, line 60-65).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 4, 7-10, 12, 13, 17 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al (US 6,146,888; see entire document) in view of in view of West et al (US 2004/0219563; see entire document). **This is a new rejection.**

Applicants claim a method of introducing a targeting vector comprising a marker gene into a cell by electroporation for homologous recombination wherein the vector does not comprise a promoter and wherein the cells are further differentiated following selection.

The teachings of Smith et al are as above. However, Smith et al do not teach that the construct is promtoerless or that the cells are differentiated following transformation.

In ¶0180, West et al state that DNA markers can be inserted into human genes by homologous recombination. The markers are either inserted into sites so that they are transcriptionally regulated by the promoters of the genes into which they are inserted (see e.g. ¶0131) or comprise exogenous promoters that are development stage specific promoter/regulatory elements (see ¶0199). In these methods it is preferable to use homologous recombination for insertion of the construct comprising a marker into a specifically selected site in a gene that is conditionally expressed in a differentiating cell to disrupt and inhibit expression of the endogenous gene to produce a knockout or inserted to be transcribed ¶0073. The method of West et al allows for isolation of cells in distinct differentiated states such that the gene profile can be determined (see e.g. ¶0199).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use targeting vectors lacking promoters as taught by West et al in the methods of

homologous recombination as taught by Smith et al because West et al teach insertion of a promoterless marker into the genome in a sight that is regulated by the stage of differentiation and Smith et al teach that it is within the ordinary skill of the art to transform a hES by electroporation with markers to identify transformed cells. Methods of inserting heterologous sequences into sequences comprising endogenous regulatory sequences were well known in the art and one would have been motivated to insert a promoterless marker into the genome in order to receive the expected benefit of using regulatory sequences known to work in the transformed cell. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARIA B. MARVICH whose telephone number is (571)272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Maria B Marvich, PhD
Examiner
Art Unit 1633

/Maria B Marvich, PhD/
Primary Examiner, Art Unit 1633